Vaccine Safety

IMMUNIZATIONS ARE AMONG THE MOST COST-EFFECTIVE AND WIDELY used public health interventions. However, no vaccine is perfectly safe or effective. As the incidence of vaccine-preventable diseases is reduced by increasing coverage with vaccines, public concerns refocus from the risk of getting disease to health risks associated with vaccines. This chapter will focus on the process of establishing and monitoring the safety of vaccines, including vaccine risk communication and evaluating and managing vaccine safety concerns. For general information about contraindications and precautions, including pregnancy and immunosuppression, refer to Chapter 2. Specific information about adverse reactions and contraindications for each vaccine may be found in chapters 4-16. Health effects reported as being associated with vaccines may be 1) true adverse reactions or 2) associated with vaccination only by coincidence. In the United States, both types of events are reported to the Vaccine Adverse Event Reporting System (VAERS), which is administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA).

Comparison of Maximum and Current Reported Morbidity Vaccine-Preventable Diseases and Vaccine Adverse Events United States

Disease	Maximum Cases	Year	1996*	Percentage Change
Diphtheria	206,939	(1921)	1	-99.99
Measles	894,134	(1941)	488	-99.95
Mumps	152,209	(1968)	658	-99.57
Pertussis	265,269	(1934)	6,467	-97.56
Polio (wild)	21,269	(1952)	0	-100.00
Rubella	57,686	(1969)	210	-99.64
Cong. Rubella Synd.	20,000+	(1964-5)	2	-99.99
Tetanus	1,560+	(1948)	27	-98.27
Invasive *Hib* Disease	20,000+	(1984)	276	-98.62
Vaccine Adverse Events	0		11,690	+++

* Provisional
\+ Estimated because no national reporting existed in the prevaccine era

Approximately 10,000 cases of adverse health effects are reported to VAERS each year. The number exceeds the current reported incidence of most vaccine-preventable childhood diseases combined, although it is still much less than the pre-vaccine era disease incidence. Close monitoring and timely assessment of suspected vaccine adverse events are critical to prevent the public's loss of confidence in vaccines. Public concerns about the safety of whole cell pertussis vaccine in the 1980's resulted in decreased vaccine coverage levels and the return of epidemic disease in Japan, Sweden, United Kingdom and several other countries.

In the U.S., similar concerns led to increases in the number of lawsuits against manufacturers and the price of vaccines, and a decrease in the number of manufacturers willing to produce vaccines.

In developing countries vaccine safety concerns are different than those in the United States. There they are more about inadequate control of vaccine production and administration errors such as reuse of needles resulting in the transmission of blood-borne pathogens. It is anticipated that as nations in both developed and developing countries reach high vaccine coverage and vaccine-preventable diseases become less visible, public concern about vaccine safety may also threaten the stability of immunization programs in developing countries.

Public health recommendations for vaccine programs and practices represents a dynamic balancing of risks and benefits. Vaccine safety or risk monitoring is necessary to accurately weigh this balance and adjust vaccination policy. This was done, for example, in the U.S. with smallpox and polio as they neared global eradication. Complications due to both vaccines exceeded that due to the disease, leading to discontinuation of routine smallpox vaccinations (prior to actual global eradication) and the shift from live oral polio vaccine to a schedule that includes only inactivated polio vaccine.

Research in vaccine safety can help to distinguish true vaccine reactions from coincidental unrelated events and may help to maintain public confidence in immunizations and the credibility of immunization programs. If immunization programs are to take full advantage of the new vaccines made possible by biotechnology, they will require an understanding of both the risks and the benefits of immunizations.

The Importance of Vaccine Safety

Importance of Vaccine Safety

- Higher standard of safety expected of vaccines
  - "First do no harm" (*primum non nocere*)
  - Moral duty: public health $\geq$ clinical medicine
  - Vaccinees generally healthy (vs. ill for drugs)
  - Vaccinations universally recommended or mandated
- Lower risk tolerance = search for rare reactions
- Studies of rare events:
  - More costly and difficult
  - Less likely to be definitive

A higher standard of safety is generally expected of vaccines than of other medical interventions because, in contrast to most pharmaceutical products which are administered to ill persons for curative purposes, vaccines are generally given to healthy persons to prevent disease. Public tolerance of adverse reactions related to products given to healthy persons, especially healthy infants, is substantially lower than to products administered to persons who are already sick. This lower risk tolerance for vaccines translates into a need to thoroughly investigate the possible causes of rare adverse events following vaccinations. High safety standards are required for vaccines because of the large number of persons who receive them including those persons who may be compelled by state or local immunization requirements for school entry. The medical maxim “first do no harm” applies even more in public health than in clinical medicine where decisions affect fewer persons.

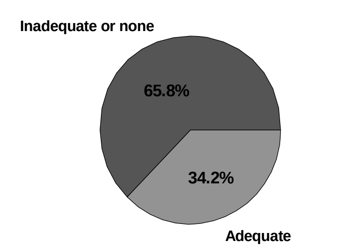
Vaccine safety studies require a higher standard of accuracy and timeliness, because of the narrow margin of error. Unlike many classes of drugs for which other effective therapy may be substituted, vaccines generally have few alternative strains or types (oral and inactivated poliovirus vaccines being the best known exceptions). The decision to withdraw a vaccine or switch between strains may also have wide ramifications. For example, the withdrawal of the 1976 “swine influenza” vaccine due to elevated risk of Guillain-Barre syndrome led to many lawsuits and low public acceptance for influenza vaccinations for a decade. Establishing associations with vaccines and promptly defining the attributable risks are critical in placing adverse events in the proper risk-benefit perspective. An erroneous association or attributable risk can undermine confidence in a vaccine and have disastrous consequences for vaccine acceptance and disease incidence. Finally, because many vaccinations are mandated for public health reasons and because no vaccine is perfectly safe, several countries have established compensation programs for persons who may have been injured by vaccination. Accurate assessments of whether adverse events can be caused by specific vaccines are required to justly compensate persons injured by true reactions and to disallow false or unrelated claims.

Limitations in Knowledge of Vaccine Safety

In 1967, the lack of scientific documentation on the hazards of immunization moved Sir Graham Wilson, former director of the Public Health Laboratory Service in the U.K., to compile the first vaccine safety review. He noted fear of compensation claims or inadvertent support to “anti-vaccionalists” as possible explanations for the incomplete records.

Adequacy of Evidence to Accept/Reject Vaccine Causality, 1991-1994

76 Vaccine Adverse Events Assessed by IOM



The National Childhood Vaccine Injury Act of 1986 established a Committee from the Institute of Medicine (IOM) to review the adverse consequences of childhood vaccines. This group found severe limits in the knowledge and research capability on vaccine safety. Of the 76 vaccine adverse events they reviewed for causal relation, 50 (66%) had no or inadequate research. Specifically, the IOM Committees identified the following limitations:

1) inadequate understanding of biologic mechanisms underlying adverse events; 2) insufficient or inconsistent information from case reports and case series;

3) inadequate size or length of follow-up of many population-based epidemiologic studies; 4) limitations of existing surveillance systems to provide persuasive evidence of causation; and 5) few experimental studies published relative to the total number of epidemiologic studies published. The IOM concluded that if research capacity and accomplishment are not improved, future reviews of vaccine safety would be hindered.

Vaccine safety research requires expertise in "rare disease" epidemiology. Such studies are costly and difficult to organize and may be less familiar to most immunization experts with mainly an infectious disease background. Like other areas of safety (e.g., food, transport), "vaccine safety" cannot be studied directly but, can be inferred by the sum of its inverse: an absence of specific problems when appropriate surveillance and risk management systems are in place. Scientifically, it is more challenging to prove than disprove a concept, especially a negative concept.

Methods of Monitoring Safety

Pre-licensure

Vaccine Safety Studies: Pre-Licensure

- Laboratory
- Animals
- Humans
  - Phases I, II, III trials
  - Sample size (<100,000s)
  - Randomized, placebo-controlled => causality assessment easy
  - Poorly detected reactions:
    - Rare
    - Delayed onset
    - Subpopulations

Vaccines, like other pharmaceutical products, undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in sequentially-phased human clinical trials prior to licensure. Phase I trials usually number in the tens and can only detect the grossest toxicity. Phase II trials generally enroll hundreds of persons and, when carefully coordinated, can provide important conclusions. These conclusions might address the relationship between the concentration of antigens, number of vaccine components, formulation technique, effect of successive doses, and profile of common reactions, which impact on the choice of the vaccines chosen for Phase III. The samples for Phase III vaccine trials are principally based on efficacy considerations. The study sample size usually ranges between 100's-10,000's participants. The duration of observation is also generally limited to one or two years. The availability of unvaccinated control groups allows medical scientists to clearly identify and observe common local and systemic reactions (e.g., injection site swelling, fever, fussiness).

Post-licensure

Because rare reactions, delayed reactions, or reactions within sub-populations may not be detected before vaccines are licensed, post-licensure (also called post-marketing) evaluation of vaccine safety is critical.

Historically, this has relied on passive surveillance and ad hoc epidemiologic studies. More recently, Phase IV trials and preestablished large-linked databases (LLDB)'s have been added to improve our methodology capabilities to study rare risks of specific immunizations. Furthermore, because vaccines are biologic rather than chemical in nature, variation in rates of adverse events (and immunogenicity), by recipient population, manufacturer, or even by lot might be expected. Post-licensure surveillance systems may detect potential lot-specific irregularities in a timely manner. Fundamental to preventing safety problems is the assurance that any vaccines for public use are made under Good Manufacturing Practices (GMP) with pre-release lot testing for safety and potency. This evaluation usually occurs in parallel to the clinical trials prior to vaccine licensure. To further assure safety, it is also critical that staff administering immunizations receive training in appropriate vaccine storage, handling, and safe injection practices.

Vaccine Safety Studies: Post-Licensure

- Spontaneous Reporting System (e.g. VAERS)
- Phase IV trials: N ~10,000, better but still limited
- Controlled Epidemiologic Studies:
  - ad hoc
  - pre-organized Large Linked Data Bases
- Causality assessment difficult:
  - appropriate (unvaccinated) controls?

Passive Surveillance (Spontaneous Reporting System)

Informal or formal passive surveillance or spontaneous reporting system (SRS) has been the cornerstone of most vaccine safety monitoring systems because of their relative low cost of operations. National reporting of vaccine adverse events can be done through the same reporting channels as those used for other adverse drug reactions. Vaccine manufacturers also maintain SRS for their products, which are usually forwarded subsequently to appropriate national authorities.

Due to the importance of infectious disease control, vaccines are purchased and administered by national public health authorities. For example, in the public sector (for example HCFA and local governments) coordinate their programs with the Centers for Disease Control and Prevention (CDC). The CDC purchases and distributes over half of the childhood vaccines administered in the United States. The FDA licenses and regulates vaccines, and collaborates with CDC in the development of vaccine adverse event reporting systems.

The Vaccine Adverse Event Reporting System (VAERS)

The National Childhood Vaccine Injury Act of 1986, mandated that 1) health care workers who administer vaccines, and 2) licensed vaccine manufactures, report certain adverse health events following specific vaccinations.

The Vaccine Adverse Event Reporting System (VAERS), jointly administered by the CDC and FDA, was created in 1990 to provide a unified national effort for the collection of all reports of clinically significant adverse events. The creation of VAERS also provided an opportunity to correct some shortcomings of the predecessor CDC Monitoring System for Adverse Events Following Immunizations (MSAEFI) and FDA's Adverse Drug Reaction.

Vaccine Adverse Event Reporting System (VAERS) (Call 1-800-822-7967)

- **Unified Spontaneous Reporting System/Passive Surveillance**
- **Operational since November 1990**
- **Co-project officers: CDC + FDA**
- **Receives ~10,000 reports/year**
- **Detect changes in:**
  - **previously known VAE (e.g., GBS)**
  - **previously unknown VAE (e.g., hep B + alopecia)**
- **Registry of rare potential VAE's**
- **?Standard followup protocols**

The VAERS reporting form is designed to allow a narrative description of adverse events. Because VAERS is an open reporting system, all persons, including patients, their parents (who submit <5% of VAERS reports) and health professionals, can report adverse events to VAERS. There are no restrictions on onset intervals or requirements for medical care. Annually VAERS forms are sent to approximately 200,000 physicians in the specialties of pediatrics, family practice, general practice, internal medicine, obstetrics/gynecology, and emergency medicine. Copies are also sent to state health departments and to public clinics that administer vaccines. Information sought on the VAERS report includes the vaccine received, the timing of the vaccination in relation to the onset of adverse events, demographic information about the recipient, information about concurrent to medical illnesses or medications, and past history of adverse events after vaccination. The form is preaddressed and postage-paid so that after completion it can be folded and mailed. **To request a VAERS form, assistance in completing the form, or answers to other questions about the reporting system, call 1-800-822-7967.**

To increase government efficiency, VAERS operations are partially "privatized." A contractor, under CDC and FDA supervision, distributes, collects, codes [using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)] and enters VAERS reports in a database. A verification-of-receipt letter, bearing the assigned VAERS identification number is returned to the reporter. Reporters of selected serious events receive written requests from VAERS (60 days after vaccination and one year after vaccination) for information about the patient's recovery. Reporters may also submit additional relevant information to the VAERS by using the assigned identification number. Both the CDC and FDA have on-line computer access to the VAERS database and focus their efforts on analytical tasks of interest to their respective agencies. These data (without personal identifiers) are also available to the public.

Since VAERS' inception, approximately 10,000 reports have been received annually, ~20% of which are defined as serious (death, disability, etc.) Due to this volume, follow-up by a health professional currently occurs on all reports of deaths and only selected serious events of interest. VAERS has successfully met its design goal as a sentinel for changes in rates of known adverse events (*e.g.*, GBS after influenza vaccination), as well as previously-unknown vaccine reactions (*e.g.*, alopecia after hepatitis B vaccine).

Classifications, case definitions and evaluative protocols

Vaccine reactions can be classified by frequency (common, rare), extent (local, systemic), severity (hospitalization, disability, death), causality, and preventability (intrinsic to vaccine, faulty production, faulty administration). A recent classification divides vaccine adverse events as follows:

1. **Vaccine-induced**: due to the intrinsic characteristic of the vaccine preparation and the individual response of the vaccinee, these events would not have occurred without vaccination (*e.g.*, vaccine-associated paralytic poliomyelitis).

2. **Vaccine-potentiated**: the event would have occurred anyway, but was precipitated by the vaccination (*e.g.*, first febrile seizure in a predisposed child).

3. **Programmatic error**: due to technical errors in vaccine preparation, handling, or administration.

4. **Coincidental**: the event was associated temporally with vaccination (*e.g.*, by chance occurrence or due to underlying illness).

To further improve the quality of SRS data and maximize its utility as a registry of rare potential vaccine reactions, standard protocols for the clinical evaluation of selected serious events reported to VAERS (*e.g.*, deaths, seizures) are under development. Such protocols could then be sent to the health care providers who report such events in order to standardize the evaluation of these patients.

Assessment of causality

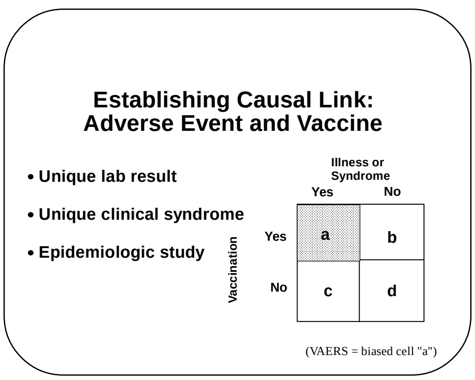
It is natural to suspect a vaccine to be the cause when an adverse event occurs following vaccination, but in reality a causal association may or may not exist. Temporal association does not prove causation.

Temporal association does not prove causation.

Information used for assessing causality in individual case reports includes: a) previous general experience with vaccine; b) alternative etiologies; c) susceptibility of the vaccinee; d) timing of events; e) characteristic of the event (*e.g.*, confirmatory laboratory findings); f) dechallenge; g) rechallenge

When it is established that a particular vaccine can cause a specific adverse reaction the next question is: what is the probability that an individual will experience the reaction, or what proportion of the vacinated population will experience it (*i.e.*, what is the attributable risk)? This information is critical for risk-benefit considerations.

Another approach to causality that minimizes controversy is to assume that adverse events that occur within a particular period after vaccinations are caused by the vaccine, irrespective of whether they were truly causal or just coincidental. This approach to causality is used in some vaccine injury compensation programs to simplify the proceedings. Classifications are based on the reported symptoms, the interval between vaccination and onset of symptoms, and a set of case definitions.



Usually, causal link between the vaccine and an adverse event can be established if there is 1) an unique laboratory diagnostic result (*e.g.*, viral culture in patient with adverse event and genetic sequencing showing virus is a vaccine and not a wild strain); 2) an unique clinical syndrome (*e.g.*, acute flaccid paralysis classical for polio occurring shortly after receipt of oral polio vaccine in setting where wild polio virus circulation is unlikely); or 3) an epidemiologic study showing vaccinated person are more likely than unvaccinated person to experience the adverse event. Unfortunately, very few VAERS reports meet either criteria 1) or 2). Since VAERS reports come from just vaccinated persons with adverse events, they represent just cell "a" of such a "2 x 2" table needed for an epidemiologic study. The information needed to complete the other 3 cells is usually missing. This explains in part the relative lack of knowledge regarding vaccine safety found by the IOM and the value of Large Linked Data Bases (LLDB's) for studying vaccine safety since all the data to complete this table are readily available via this approach.

Large-Linked Databases (LLDB)

Historically, when a signal of a potential vaccine safety concern was generated from passive surveillance, ad hoc epidemiologic studies were needed to test this hypothesis.

Such ad hoc studies, while potentially informative about vaccine causality, were costly, time-consuming, and usually limited to assessment of a single event. The need to improve post-licensure monitoring of drug safety became widely recognized following the thalidomide disaster. Faced with methodology limitations in passive surveillance for drug adverse events, pharmacoepidemiologists during the 1980s began to turn to large databases linking computerized pharmacy prescription (and later, immunization records) and computerized medical outcomes (*e.g.*, hospitalization) records. These LLDBs are derived from defined populations such as members of health maintenance organizations (HMOs), single-provider health care systems, and Medicaid programs. As these databases are usually generated in the routine administration of such programs and do not require completion of a vaccine adverse event reporting form, the problems of under-reporting or recall bias are reduced. Therefore, LLDBs can potentially provide an economical and rapid to means of conducting post licensure studies of safety of drugs and vaccines. CDC's Vaccine Safety Datalink (VSD) project is one example of such a LLDB. It links the immunization and medical records on members of four HMO's, totalling 2% of the US population for various vaccine safety studies.

Vaccine Safety Datalink (VSD)

- **Popul. under "active suveillance"**
  - **6 million enrollees in 4 HMO's**
  - **2% US population**
- **Large-Linked Databases**
  - **Exposure (vaccination)**
  - **Outcome (ER, OPD, hosp, lab)**
  - **Covariates (birth, death certificates)**
- **Uses:**
  - **scientific rigorous hypo "testing"**
  - **if causal => Vaccine Injury Table**
    - **attributable risk => risk comm**
    - **risk factors => contraindications**

Another method to effectively track vaccines and vaccine lot numbers is immunization registries. Registries are confidential, population-based, computerized information systems that contain information about immunizations and children who receive them. An immunization registry provides an automated means of efficiently tracking and easily accessing this information. While all states are engaged in registry activity, currently 35 states have implemented their registries. To find out if your state has a immunization registry call (800) 799-7062.

Vaccine Risk Communication

Disease prevention, especially when it requires high compliance by the population, is a difficult task. In the pre-immunization era, vaccine preventable diseases like measles and pertussis were so widespread that the risks and benefits of disease versus vaccination were readily evident. As immunization programs successfully reduced the incidence of disease, an increasing number of health care providers and parents, have had little or no personal experience with these diseases. For their risk benefit analysis, these individuals are forced to rely on history, and other more "distant" descriptions of these diseases in textbooks or educational brochures. In contrast, what is visible is the degree of very personal discomfort and pain associated with each immunization.

Other social factors also mitigate against timely vaccination, for example, biased and inaccurate reporting by controversy-seeking media, increasing popularity of “alternative” medicine, and inaccurate information relating to vaccines posted on the Internet and in some books. Because of these factors the art of handling vaccine safety concerns and vaccine risk communications has emerged as an increasingly important skill for clinicians and for managers of immunization programs.

Risk communication principles

Vaccine Risk Communication Principles

- **perceptions of risk depend on:**
  - **individual personality, education, and life experience**
  - **who is the "stakeholder"?**
- **acceptability or risk depend on:**
  - **voluntariness of risk decision**
  - **"omission" bias (inaction > action)**
- **uncertainty => patient rely on advice of trusted health care professional**

The science of risk communication was developed initially to address public concerns in areas of technology and environmental risks. Some key principles and lessons include the following: 1) individuals differ in their perceptions of risk depending on their personality, education, and life experience, 2) perceptions of risk may differ dramatically, depending on the person's perspective (*e.g.*, as a public health employee, vaccine industry representative, alternative medicine practitioner, average parent, or parent of a vaccine-injured child); 3) “voluntary” risks (*e.g.*, driving a car) are usually more acceptable than involuntary risks (*e.g.*, mandated immunizations); risk comparison examples used for educational purposes that fail to take the degree of voluntariness into account can back fire and create anger. 4) many persons have an “omission bias” in that they prefer the consequences of inaction (not receiving vaccinations) to action (receiving vaccinations); 5) patients frequently rely on the advice of their physician or other health care professional for guidance about risks and benefits of vaccination.

In the U.S., distribution of information, developed by the CDC, about the risks and benefits of immunizations has been required in the public sector since 1978. Distribution of such material in both private and public sectors has been required since 1988. Recent efforts have been devoted toward the use of focus groups and other research to assess and improve the effectiveness of such information material.

In many countries including the U.S., persons who believe that they or their children have been injured by vaccines have organized to distribute information that highlights the risks of and uncertainties related to immunizations through the Internet and various publications. Materials to address these misconceptions and allegations about immunizations are developed and distributed to state immunization programs, partners and the public as they arise.

Some useful resources include the National Immunization Information Hotline (800-232-2522), the National Immunization Program Website (www.cdc.gov/nip) and the CDC publication entitled *6 Common Misconceptions about Vaccination and How to Respond to Them* (see Appendix F). In the future, we will need to create better systems to develop and disseminate vaccine safety materials to immunization providers in a timely manner. It will also be necessary to develop historically based materials that express the impact outbreaks of vaccine preventable diseases have had on the death and disability of countless individuals and families.

Risk communication can be used for the purposes of advocacy, public education, or decision-making partnership. People care not only about the magnitude of the risk, but also how the risks are managed and whether they participate in the risk management process, especially in a democratic society. Receiving a vaccination is unlike most other medical procedures (*e.g.*, surgery), in that the consequences of the decision affect not only the individual, but also others in the society. Because of this important distinction, many countries have enacted public health (e.g., immunization) laws that severely limit any individual's right to infect others. Some persons may attempt to avoid the risks of vaccination while being protected by the group (or herd) immunity, which results from others being vaccinated. The protection provided by herd immunity may disappear if too many persons avoid vaccination, which may result in tragic outbreaks of diseases. Recent debates in the U.S. have focused on whether philosophical (in addition to medical and religious) exemptions to mandatory immunizations should be allowed more universally, and if so, what standards for claims of exemption are needed. Vaccine risk communications should discuss the risks and benefits of specific vaccines, and should also inform persons receiving vaccinations about the delicate balance between societal and individual rights in a shared community.

Evaluating and Managing Vaccine Safety Concerns

Healthy doses of empathy, patience, and scientific skepticism, are all needed to effectively address vaccine safety concerns from a clinical perspective. As with all investigations, the first step is objective and comprehensive data gathering with an open mind. Premature dismissal of new vaccine safety concerns as "unfounded" without gathering and weighing the evidence is unwise and unscientific.

Periodically, vaccine safety concerns may emerge in the media. Because media frequently aims to present both sides of the story as equal in impact and importance, the challenge for health care professionals is to establish greater credibility to the audience. Factors that aid in such credibility include scientific expertise, relationship with media on prior difficult issues, empathy, and ability to distill scientific facts and figures down to easily understood concepts for persons who may not have medical or scientific training. Emotionally compelling first hand accounts of persons with vaccine preventable diseases may be needed to effectively illustrate the importance of vaccination practices. Clarifying the distinction between perceived and real risk for the concerned public is critical. What is certain is the increased risk of illness should a person choose not to be vaccinated. What is also certain is the small magnitnude of any severe vaccine reactions should they exist.

Vaccine Safety: Summary

- **Vaccine safety concerns increasingly prominent**
  - **success of vaccines in reducing VPD**
  - **few providers/parents have experience with VPD**
- **Data gaps in vaccine safety exist**
  - **Research underway to fill the gaps**
  - **Serious reactions are rare**
- **Risk communications on the benefits and risks of vaccination critical**

Selected References

See Appendix F for Vaccine Safety references.